

PARTICLE CASSETTE, METHOD AND KIT THEREFOR

Technical Field of the Invention:

The present invention relates generally to the retention of particles prior to the
5 needleless injection of those particles in a gas stream. More specifically, the present
invention relates to particle cassettes having a pair of membranes which retain the particles
in a chamber therebetween.

Background to the Invention:

10 Needleless syringe devices are known from WO 94/24263. In this document, a
needleless syringe is disclosed which entrains particles in a gas stream accelerated through
a nozzle so that the particles may be injected into a target, such as human skin or other
cells. For many applications, there is a need for the particles to be maintained in a sterile
environment prior to actuation of the device. WO 94/24263 discloses for this purpose a
15 particle cassette comprising a central annular ring having rupturable diaphragms sealed to
each face so as to form a self contained sealed unit containing the particles to be injected.
Upon actuation of the device, the diaphragms rupture allowing the particles initially
contained between the diaphragms to be entrained in the gas flow and then delivered into
the target.

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Summary of the Invention:

Figures 1a to 1d of the accompanying schematic drawings show steps in the
manufacture of the particle cassette disclosed WO 94/24263. A substantially annular ring
(10) is shown in axi-symmetric cross-section in Figure 1a. The ring has an open central
25 section defining a chamber (11). In a first step of the manufacturing process a rupturable
diaphragm (12) is sealed to the bottom face of the annular ring (10). This results in the
construction shown in Figure 1b. Then, as shown in Figure 1c, particles (13) are supplied
to the chamber (11). The particles (13) so supplied are those to be injected into the target.

The last stage in manufacture comprises sealing a second membrane (14) onto the other face of the annular ring so as to seal the particles (13) within the central chamber (11).

The cassette can then be handled while the particles are maintained in a sterile environment. During actuation of the needleless syringe, a gaseous pressure is applied to one of the membranes (12, 14) such that the membrane bursts and the gas entrains the particles. Shortly afterwards, the other membrane bursts so that the gas (with the particles entrained) can be accelerated in a nozzle and thence into a target.

WO 94/24263 discloses that the diaphragm should preferably be heat sealed to the faces of the annular ring. Heat sealing has been found to be a particularly easy and repeatable method of sealing the diaphragms to the ring of the cassette body.

It has been found that the above-mentioned configuration has a disadvantage associated with its manufacture, which may become especially deleterious when heat-sensitive powdered drug particles are to be carried by the cassette. After the particles have been supplied to the chamber (11) formed by the annular ring (10) and the bottom membrane (12), the heat sealing of the top membrane (14) onto the ring (10) can sometimes result in a degradation of the particles. This degradation may take the form of melting, causing particle deformation, particle agglomeration and other undesirable physical and chemical changes in the product. Further, the melt may affect the therapeutic effect of the particles.

Accordingly, the present invention therefore seeks to alleviate this problem by providing a particle cassette, a kit of parts and a method for the manufacture therefor in which the possibility of the particles melting during manufacture is much reduced.

In accordance with the first aspect of the present invention, there is provided a kit of parts for use in the manufacture of a particle cassette for a needleless syringe device, said kit comprising:

a first cassette part having a first rupturable membrane sealed thereto; and

a second cassette part having a second rupturable membrane sealed thereto; said first and second cassette parts being arranged to be attachable together so as to create a chamber for the confinement of particles between said first and second membranes.

Thus, since the membranes are sealed to first and second cassette parts (possibly by heat sealing) before the particles are supplied to either of the cassette parts, there is a much reduced possibility of the membrane heat sealing process influencing the particle condition or composition. Further, the invention provides a quick and easy method of manufacturing a particle cassette and has these advantages over processes which do not involve heat sealing.

Preferably, the first and second cassette parts are annular such that the second part is attachable concentrically around the first cassette part. This allows the first cassette part to extend substantially along the whole width of the particle cassette making it easier to fill the first part with particles prior to attaching the second part.

To attach the first and second parts together, a variety of mechanisms may be used, including interference fits, friction fits, detents and recesses, close tolerances, gluing etc. Preferably, however, a snap fit is provided for by arranging corresponding features on each of the first and second parts (for example a detent and a recess).

In order to ensure a consistent width of particle cassette, it is preferable to provide a seating face on each of the first and second parts, such a seating face providing a minimum possible width of particle cassette when assembled.

A tapered face on each of the first and second parts allows the parts to be brought together easily during assembly.

A third cassette part may be used to attach the first and second parts together. In a preferred embodiment, the third cassette part is inserted in an annular apace between the first and second cassette parts, to provide a secure attachment (or "locking"). The third part preferably has a third membrane to ensure sterility and may be provided with one or more protrusions to ensure an interference fit with the second cassette part.

In a second aspect of the invention, there is provided a particle cassette for a needleless syringe comprising an assembled kit according to the first aspect and particles provided in the chamber between the first and second membranes.

According to a third aspect of the present invention, there is provided a needleless syringe including the particle cassette of the second aspect of the invention.

According to a fourth aspect of the invention, there is provided a method of assembling a particle cassette for a needleless syringe device, said method comprising:

- (a) sealing a first rupturable membrane to a first cassette part;
- (b) sealing a second rupturable membrane to a second cassette part;
- 5 (c) applying particles to said first cassette part;
- (d) attaching said first and second cassette parts together so as to create a chamber confining said supplied particles between said first and second membranes.

The sealing of the membranes to the cassette parts independently from the
10 steps of supplying particles to one of the cassette parts and attaching the cassette parts together ensures that the method used for sealing the membranes to the cassette parts does not unduly influence the quality of the particles in the cassette.

Preferably, attaching step (d) does not involve the application of any heat at all and it is preferably carried out at the same temperature as supplying step (c) to ensure that the
15 particles are not affected by the step of attaching the first and second cassette parts together.

It is not essential that supplying step (c) is carried out after sealing step (b) since the second membrane may be sealed to the second cassette part after the particles have been supplied to the first cassette part.

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Brief Description of the Drawings:

Embodiments of the present invention will now be described, by way of example only, with reference to the accompanying schematic drawings, in which:-

Figures 1a to 1d are cross-sectional views showing stages in the manufacture of a
25 particle cassette according to the prior art;

Figures 2a and 2b are cross-sectional views showing stages in the manufacture of a particle cassette according to a first embodiment of the invention;

Figure 3 is a cross-sectional view showing an assembled particle cassette according to a second embodiment of the present invention;

Figure 4 is a cross-sectional view showing an assembled particle cassette according to a third embodiment of the present invention;

Figure 5 is a cross-sectional view showing an assembled particle cassette according to a fourth embodiment of the present invention;

5 Figure 6 is a cross-sectional view showing an assembled particle cassette according to a fifth embodiment of the present invention;

Figure 7 is a cross-sectional view of a second cassette part according to a sixth embodiment of the present invention;

10 Figure 8 is a cross-sectional view of a first cassette part according to a sixth embodiment of the present invention;

Figure 9 is a cross-sectional view along the line A-A shown in Figure 8;

Figure 10 is a cross-sectional view of a third cassette part according to a sixth embodiment of the present invention;

15 Figure 11 is a cross-sectional view of an assembled particle cassette according to a sixth embodiment of the present invention; and

Figure 12 shows two perspective views of a partially cut-away particle cassette according to the sixth embodiment of the present invention.

Description of Preferred Embodiments:

20 In the drawings the components are not drawn to scale. The drawings are schematic for reasons of clarity. In reality the thickness of the rupturable diaphragms may be much less than that shown and/or the volume of particles may be so small as barely to be visible to the naked eye.

25 The present invention avoids the possibility of the heat sealing of the membranes affecting the particle quality by ensuring that the particles are confined within the chamber of the cassette by a step other than one involving heat sealing of one of the membranes. Thus, generally speaking, each of the embodiments of the present invention comprises a first cassette part (20) having a first membrane (22) sealed to a face and a second cassette part (21) having a second membrane (23) sealed to a face. Particles (24) are dispensed

into the first cassette part and the second cassette part is then attached. The attachment step should not involve the application of an amount of heat such as is likely to damage the particles. However, heat sealing can be used in the attachment step if the heat is used such that the particles are not likely to be damaged.

5 Figures 2a and 2b show an axi-symmetric cross-section of the particle cassette according to the first embodiment of the present invention.

 In the first embodiment, the first cassette part (20) comprises an annular ring having a first face (the upper face in Figure 2a) for attachment to a second cassette part (21), the other side of the annular ring having had a first membrane (22) sealed thereto. The second
10 cassette part (21) is substantially identical to the first cassette part, having had a second membrane (23) sealed thereto. The first and second cassette parts, having the first and second membranes respectively, form a kit of parts for use in the manufacture of the particle cassette. The membranes are sealed to the external faces of the respective cassette parts. If heat sealing is used to attach the membranes then a recess (30,31) as
15 shown in Figure 2a is useful because it allows for some plastic deformation as will be caused by heat sealing in general. In particular, the heat causes local expansion of the cassette material and the recesses (30,31) allow the cassette material to expand without affecting the designed gas flow path (eg by restricting the diameter of the flow path).

 In order to manufacture the particle cassette, particles (24) are dispensed to the
20 first cassette part (20) and the first (20) and second (21) cassette parts are attached together so as to create a closed chamber for the confinement of the particles (24) between the first (22) and second (23) membranes. The assembled particle cassette is shown in Figure 2b.

 In use, the particle cassette is located in a needleless syringe device which may
25 have the general construction, and method of operation, described in WO 94/24263 or WO 01/05455, the contents of which are hereby incorporated by way of reference. When located in the syringe device the device construction is advantageously such as to prevent the first cassette part (20) coming away from the second cassette part (21). However, in order to mitigate against further such detachment, the second cassette part

(21) may be adhered to the first cassette part (20), for example by gluing or by taping around the external circumference of the particle cassette. This provides a sealed unit of particles which can be handled outside of the needleless syringe device with reduced possibility of particles escaping from between the two cassette halves.

5 A second embodiment of the invention is shown in Figure 3. The particles (24) are omitted from inside the particle cassette for the sake of clarity. Further, it is to be noted that the particle cassette shown in Figure 3 (and those shown in Figures 4 to 6 as well) will, prior to assembly, make up a kit of parts according to the first aspect of the present invention.

10 In the second embodiment, the first cassette part (20) is constituted by a substantially annular member which extends to a height X nearly equal to the height Y of the assembled particle cassette. This greatly facilitates the filling of the first cassette part (21) with particles (24) since a larger receptacle than is provided in the first embodiment can be used to receive particles (24). A further advantage is that the whole internal volume
15 of the cassette can be used to hold particles. In contrast, the first embodiment can only be half filled with particles since the first cassette part (20) has a height equivalent only to approximately half the final height of the cassette.

The second cassette part (21) also has a substantially annular construction and is arranged to be attachable concentrically around the first cassette part (20). If necessary,
20 adhesive can be used at the interface (25) to ensure that the first and second cassette parts do not detach easily. More preferred, however, is that the cassette parts are attached by an interference fit, whereby the outer diameter of the engaging region of the first cassette part is slightly larger than the inner diameter of the engaging region of the second cassette part (21). In this way, the parts will naturally lock together due to the elastic strain
25 established in each of the first and second cassette parts when the second part (21) is placed around the first part (20).

The second embodiment shown above has advantages over the first embodiment because it does not necessarily require an extra adhesive to be used (an interference fit is instead used) and because the first cassette part defines a larger receptacle area for

receiving the particles (24). However, the second embodiment has the disadvantage that it may be difficult or fiddly to assemble, even if one or both of the engaging inner face of the second cassette part and the engaging outer face of the first cassette part is provided with a lead in taper to aid assembly. To overcome this problem, a cassette according to the third embodiment of the invention is provided. Such a cassette is shown in Figure 4.

In the third embodiment of the present invention, the outer engaging face of the first cassette part (20) and the inner engaging face of the second cassette part (21) (the interface of which is denoted as (26) in Figure 4) are tapered so as to allow the second cassette part (21) to be easily placed over the first cassette part (20). Again, although gluing may be used to attach the parts, it is preferable that the first cassette part (20) has a larger outer diameter than the inner diameter of the second cassette part (21) at each point along the height of the cassette. This means that as the parts are brought close to the assembled position shown in Figure 4, some elastic strain is established in the parts to provide a snug fit. The parts are prevented from coming apart by friction along the tapered interface (26).

The third embodiment of the invention thus has the advantage that it is easier to assemble the kit of parts than the second embodiment of the invention. However, it has the potential disadvantage that the width of the cassette (ie the vertical dimension in Figure 4) may not necessarily be predicted before the parts are assembled. Depending on the force used to push the first (20) and second (21) cassette parts together, the width may vary over a certain range. For example, if the parts are pressed together very strongly, the width is likely to be less than if the parts are only lightly pressed together. Furthermore, the leading edge of the first cassette part (20) may damage the seal between the second membrane (23) and the second cassette part (21) if the two parts are pushed together too strongly.

To overcome this problem, a particle cassette as shown in the fourth embodiment of the invention is provided.

In this embodiment, a seating face (27) is provided to each of the first (20) and second (21) cassette parts. As is shown in Figure 5, once the cassette parts have been

pushed together a certain amount, the seating face (27) prevents further movement in the cassette height direction (i.e. the vertical direction in Figure 5). The fourth embodiment of the invention therefore allows the width dimension of the assembled particle cassette to be reliably ensured. The tapered sections (26) perform the same function as in the third
5 embodiment and the outer surfaces of the first cassette part (20) may again be made to have a slightly larger diameter than the inner surfaces of the second cassette part (21) so as to provide an interference fit. The steeper angle of the lower tapered section 26 provides for a better locked fit. The fairly uniform cross-section in the vicinity of the membranes allows for good heat dissipation during the heat sealing process, if used.

10 While an interference fit is suitable for a lot of purposes, it is often preferable that no elastic strains are built up in the first and second cassette parts, especially if they are to be re-used a lot of times. The fifth embodiment of the invention addresses this problem. Figure 6 shows an axi-symmetric cross-sectional view of the fifth embodiment of the invention having parts generally similar to those shown in Figure 5.

15 The main difference is the provision on each of the first (20) and second (21) cassette parts of corresponding features (28, 29) which provide for a snap fit when the first and second cassette parts are brought together. In particular, the first cassette part (20) comprises a detent (28) located on one of external tapered surfaces (26).

Correspondingly, the second cassette part (21) comprises a recess (29) on its respective
20 tapered surface (26). Thus, when the first and second cassette parts are brought together, the detent (28) locates in the recess (29) to lock the two pieces together. During this attaching step, both the first and second cassette parts undergo a momentary elastic strain as the detent (28) engages in the recess (29) but, once assembled, the cassette part can be arranged so that there is little residual strain present. This means that there is no

25 requirement to rely on an interference fit alone to maintain the first and second cassette parts in attachment. The provision of corresponding features also makes it more difficult for the first and second parts to be accidentally detached, providing a stronger lock between the first and second cassette parts and thus a more secure sealed environment for the particles. This is particularly useful when the cassette is to be subject to vibrations,

such as those experienced during transportation. The fifth embodiment shown in Figure 6 is considered to be the best mode of carrying out the invention.

The fifth embodiment has a further advantage in that it provides an assembly that is tamper evident. Once assembled, it is very difficult to prise the cassette parts apart due to the taper lock and detent arrangement. Thus, the assembly could only be opened by destroying one of the membranes or using a very sharp tool to lever apart the parts, which in practice causes obvious deformation of the cassette parts.

Figures 7 to 12 show a sixth embodiment of the invention. Unlike the previous embodiments, the particle cassette of the sixth embodiment has three main component parts rather than two.

Figures 7 and 8 show in cross-sectional view second and first cassette parts respectively. The second cassette part (30) of Figure 7 is generally cylindrical in configuration having substantially vertical inside walls (33) and (34). The inside wall (33) has a slightly smaller diameter than inside wall (34) for reasons that will become apparent later. A shoulder portion (31) is provided adjacent a seating face (32). The shoulder portion (31) is designed to interact with the external surface of the first cassette part (40), described hereafter. A recess (35) is provided at the top end of the second cassette part (30) and this recess (35) aids in assembling the cassette.

Figure 8 shows a first cassette part (40) according to the sixth embodiment of the present invention. The first cassette part (40) comprises a substantially annular member defining within its confines a receptacle for receiving particles. The first cassette part (40) has generally cylindrical outer walls (42) and a slightly tapered seating face (41) at its bottom end. The seating face (41) is intended to rest against the seating face (32) of the second cassette part (30) during use. Furthermore, the shoulder (31) of the second cassette part (30) is intended to abut the outer surface (42) of the first cassette part to provide an interference fit. This configuration is shown in Figure 11.

Referring back to Figures 8 and 9, there are openings (43) on the inner surface of the first cassette part (40) and openings (44) on the outer surface of the first cassette part (40). These openings are connected by transfer ducts such that gas surrounding the first

cassette part (40) may enter the receptacle for receiving particles. The transfer ducts are substantially conical and are angled in three dimensions such that when gas flows therethrough a sonic jet is formed which tends to create a swirling gas movement inside the chamber confining the particles. The transfer ducts are angled such that the gas tends to

5 impinge against the membranes located at either side of the first cassette part (40). Furthermore, the holes (43) are provided at different longitudinal ends of the first cassette part (40) and are directed in different directions such that a clockwise gas flow is established at one end of the particle confinement chamber and an anti-clockwise gas flow is established at the other end of the particle confinement chamber. This is illustrated in

10 Figure 12 wherein the gas flows are referenced (65) and (66). As is clear from Figure 9, the transfer ducts are provided on the same lateral side of the first cassette part (i.e. above the centre line shown in Figure 9), and this has been found to provide for good fluidization of the particles when gas pressure is introduced to the openings (44) and a flow of gas is established through the transfer ducts. However, other configurations of transfer duct in

15 the side walls of the first particle cassette part (40) can provide good results and it is not generally essential for the present invention that the transfer ducts have the specific form shown in Figures 8 and 9.

Figure 10 shows a third particle cassette part in accordance with the sixth embodiment of the present invention.

20 The third cassette part (50), in common with the first and second cassette parts, has generally cylindrical inner and outer walls forming an annular-shaped member. One or more protrusions (51) may be formed on the outer walls and these are intended to provide an interference fit against the inner wall (34) of the second cassette part (30), when the particle cassette is assembled. The lower end of the third cassette part (50) has a number

25 of formations (52) around the circumference. The formations (52) are stepped and are designed such that the top part (53) of the formations (52) abuts the top surface of the first cassette part (40) when assembled, as shown in Figure 11. The formations are spaced apart by vent holes (54) that are formed such that gas may pass through the vent holes (54) when the first and third cassette parts are attached together. The formations (52) are

shaped so as to grip, by means of friction, or interference, the top part of the first cassette part (40).

The particle cassette according to the sixth embodiment of the invention takes the form shown in Figure 11 when assembled. In this embodiment, there are three membranes
5 (61, 62, 63) of which one membrane (61) is relatively thin with a fairly low bursting pressure and is designed to keep the unit sterile in use.

To assemble the particle cassette of the sixth embodiment, a first membrane (62) is heat sealed or bonded to the upper edge of the first cassette part (40). Similarly, the second membranes (63) is heat sealed or bonded to the seating face (32) of the second
10 cassette part (30). The third membrane (61) is heat sealed or bonded to the upper face of the third cassette part (50). The first membrane and first cassette part thus define a receptacle in which the particles may be contained. The openings (43) are very small such that it is very difficult for the particles to pass out of the chamber once inside. Once the particles have been supplied to the chamber of the first cassette part (40), the first cassette
15 part (40) is brought together with the second cassette part (30) with the leading edge of the first cassette part engaging the shoulders (31) of the second cassette part. The first cassette part (40) is pushed home until the seating face (41) of the first cassette part abuts the seating face (32) of the second cassette part (with the second membrane (63) between the two seating faces). In this configuration, the particles are trapped between the first and
20 second membranes. The third cassette part (50) having the third membrane (61) thereon is then pushed in so that the formations (52) slide into the annular gap created between the first and second cassette parts. Interference and/or friction ensure that this movement firmly secures the first and second parts together and effectively "locks" the cassette. It will be appreciated that it is quite difficult to remove the third cassette part once it is
25 installed, especially if the top face (55) of the third cassette part is dimensioned so as to be flush with the top face of the second cassette part when assembled (this is not shown in Figure 11 however).

The membrane (61) ensures that the particles inside the cassette may not come into contact with any external particles or gases and thus the membrane (61) ensures the

sterility of the cassette.

In use, the cassette is inserted into a needleless syringe and gas pressure is supplied to the third membrane (61). The membrane (61) bursts quite easily and gas enters the internal space defined by the third cassette part. Gas is able to flow through the vents (54) and into the annular space (67) between the first cassette part and the second cassette part. From there, gas may pass through the transfer ducts and out through the openings (43) into the particle containment chamber. The jets of gas so formed cause the particles to be fluidized and mixed. Following that, the upstream membrane (62) bursts and the particles are entrained in the bulk of the gas flow followed by the bursting of the downstream membrane (63) shortly thereafter. In this way, the particle cassette of the sixth embodiment provides for pre-mixing and fluidizing of the particles whilst still overcoming the problem that heat sealing of membranes can damage particles when a single piece cassette is used.

The concepts described in relation to the first to fifth embodiments may also be applied to the sixth embodiment in the same way. For example, a snap fit may be provided for if detents and corresponding recesses are provided on either the first and second, first and third or second and third cassette parts respectively.

Heat sealing or adhesive is not necessary in the sixth embodiment and the first and second membranes may be sealed against the first and second cassette parts respectively due to the tight fit between the various cassette parts. For example, the first membrane (62) may be sealed by virtue of being trapped between the first and third cassette parts. Similarly, the second membrane (63) may be trapped between the first and second cassette parts, with no special heat sealing or adhesive step being required.

For each of the embodiments, the materials used to manufacture the cassette parts and the membranes may be conventional, for example, the membranes may be Mylar as disclosed in WO 94/24263 and the first and second cassette parts are preferably manufactured from a plastics material, using injection moulding for example. Both the membranes and cassette parts may be made from polycarbonate such as Evaxone 260 (EVA) polymer. If heat sealing is used, a temperature of 110°C and pressure of 760 kPa

1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464	1465	1466	1467	1468	1469	1470	1471	1472	1473	1474	1475	1476	1477	1478	1479	1480	1481	1482	1483	1484	1485	1486	1487	1488	1489	1490	1491	1492	1493	1494	1495	1496	1497	1498	1499	1500	1501	1502	1503	1504	1505	1506	1507	1508	1509	1510	1511	1512	1513	1514	1515	1516	1517	1518	1519	1520	1521	1522	1523	1524	1525	1526	1527	1528	1529	1530</
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